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Long-term Sequelae From Acute Exposure to Chlorine Gas: A Review

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Abstract

Chlorine (Cl_2; CASRN 7782-50-5) was the first gas to be used as a chemical warfare agent during the First World War and is widely utilised today in industry (e.g. oxidizing agent in water treatment; pulp mills). The immediate effects from acute exposure are well documented but the long term sequelae from an acute exposure are not well understood. Several studies were reviewed that discuss the long term outcome of an acute exposure to chlorine gas and their conclusions appear contradictory. This may be due to different endpoints being assessed, to the existence of lung diseases prior to exposure, or even the effects of smoking. The concentration and duration of chlorine exposure would also play a role in the potential for long term sequelae and few of the studies reviewed provided this information. Animal inhalation toxicology experiments that studied the potential for long term effects after an acute exposure to chlorine noted that the observed effects may resolve over time. An intrinsic limitation of animal studies is the difficulty of extrapolating to humans. Thus, from peer-review human and animal literature, it is difficult to conclusively determine if there are long term effects after an acute exposure to chlorine gas.

Résumé

Le chlore (Cl_2; CASRN 7782-50-5) est le premier gaz à avoir été utilisé comme agent de guerre chimique durant la première guerre mondiale et il est encore très utilisé dans l'industrie (par ex. : comme agent oxydant pour l'épuration de l'eau; dans les usines de pâte à papier). Les effets immédiats dus à une exposition aiguë ont été bien documentés mais les séquelles à long terme de cette exposition aiguë ne sont pas bien compris. Plusieurs des études discutant des résultats à long terme d'une exposition aiguë au chlore gazeux ont été réexaminées et leurs conclusions semblent contradictoires. Ceci est peut-être dû au fait que des effets différents ont été évalués, que des maladies pulmonaires existaient antérieurement à l'exposition ou qu'il existait des effets dus à la cigarette. Le niveau et la durée de l'exposition au chlore peuvent aussi jouer un rôle dans la possibilité des séquelles à long terme mais peu d'études réexaminées ont procuré ces informations. Les expériences en toxicologie des inhalations chez les animaux ayant examiné le potentiel des effets à long terme après une exposition aiguë ont fait remarquer que les effets observés peuvent se dissiper avec le temps. Une limite intrinsèque aux études sur les animaux est qu'il est difficile d'extrapoler les résultats pour les appliquer aux humains. Ainsi, le réexamen par des pairs de la documentation sur les humains et les animaux ne permet pas d'établir irréfutablement qu'il existe des effets à long terme après une exposition aiguë au chlore gazeux.

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Executive summary

Chlorine gas was the first war gas used during World War I and today represents an occupational risk due to its wide use in industrial settings. But it is not only industrial workers who are potentially at risk. Chlorine gas may be generated from inappropriate use of home cleaning chemicals. The objective of this report is to examine peer-reviewed literature for information on the long-term effects after a single, or acute, exposure to chlorine gas where that exposure produced immediate adverse effects.

Acute exposure to chlorine gas results in well described effects based on the exposure level of chlorine and duration of exposure. These effects range from mild irritation (nose, eyes, airways) to chest pains, shortness of breath, coughing and vomiting and death if the exposure concentration is high enough. Because chlorine is widely used in industrial processes, there is a large body of human data available for analysis. Exposure concentrations and duration of exposure are unknown for most of the studies, but all indicated that exposed individuals had immediate effects from the chlorine gas. After cessation of the acute symptoms, the follow-up was less clear. Some authors observed continued alterations in lung function or pathology, while others observed no long-term effects due to the chlorine exposure. The existence of pre-exposure diseases or conditions and the effects of smoking may have confounded the results observed. Only one study was found where pre-exposure measurements were made and the results from that study were inconclusive. It is unclear from the literature whether a single acute exposure to chlorine gas will result in long term effects after the short term effects have subsided. When the animal toxicology literature was surveyed for studies that were looking at long term effects, the results were also unclear. In many of the animals, the effects appear to be resolved over time.

In terms of chronic low-level exposures to chlorine, existing human studies suggest clear effects are impossible to measure. Furthermore, there are no known reproductive or carcinogenic effects attributable to chlorine gas exposure.

Due to the pervasiveness of chlorine in the industrial setting and the irritant properties of chlorine gas, there are numerous guidelines and exposure limits from occupational and emergency response organizations.

After reviewing the current literature on chlorine toxicity, the report concludes by noting the difficulty in definitively determining whether there are long-term effects of a single, acute exposure to chlorine gas.

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Sommaire

Le chlore gazeux a été le premier gaz à être utilisé durant la première guerre mondiale et il représente encore aujourd'hui un danger pour les travailleurs, étant donné qu'il est souvent utilisé dans le milieu industriel. Le chlore gazeux peut être généré par l'utilisation incorrecte des produits de nettoyage domestiques chimiques. L'objectif de cet article est d'examiner la documentation qui a été revue par des pairs et d'en tirer des informations au sujet des effets à long terme, après une seule exposition ou une exposition aiguë au chlore gazeux, dans le cas où cette exposition aurait produit des effets néfastes immédiats. L'exposition aiguë au chlore gazeux produit des effets bien décrits, basés sur le niveau d'exposition au chlore et sur la durée de cette exposition. Ces effets varient d'une irritation mineure (nez, yeux, voies respiratoires) à des douleurs thoraciques, essoufflements, toux, vomissements et peuvent causer la mort si le niveau d'exposition est assez haut. Le chlore étant souvent utilisé dans les procédés industriels, il existe un vaste ensemble de données humaines disponibles pour les analyses. Les niveaux d'exposition et durées d'exposition sont inconnus dans la plupart des études mais toutes ces dernières indiquent que les individus exposés au chlore gazeux ont souffert d'effets immédiats. Après l'arrêt des symptômes graves, le suivi est moins évident. Certains auteurs ont observé une altération du fonctionnement des poumons ou une pathologie alors que d'autres n'ont observé aucun effet à long terme, dus à l'exposition au chlore. L'existence de maladies ou d'un état, préalables à l'exposition, et les effets de la cigarette ont pu obscurcir les résultats observés. On n'a trouvé qu'une seule étude ayant effectué des mesures préalablement à l'exposition et les résultats de cette étude ne sont pas concluants. Il n'est pas évident, à partir de cette documentation, qu'une seule exposition aiguë au chlore gazeux produit des effets à long terme après que les effets à court terme aient diminué. La documentation sur la toxicologie chez les animaux a été examinée, pour des études faisant une recherche sur les effets à long terme, mais les résultats n'ont pas été plus évidents. Chez la plupart des animaux, les effets semblent se dissiper avec le temps.

En termes d'expositions de bas niveau et d'expositions chroniques au chlore, les études existantes chez les humains suggèrent qu'il est impossible de mesurer des effets qui soient manifestes. De plus, on ne connaît aucun effet sur la reproduction ou carcinogène qui soit attribué à l'exposition au chlore gazeux.

Étant donné l'omniprésence du chlore dans le milieu industriel et les propriétés irritantes du chlore gazeux, il existe de nombreux règlements et de nombreuses limites à l'exposition, provenant d'organismes professionnels et d'intervention d'urgence.

Après avoir examiné la documentation actuelle sur la toxicité du chlore, l'article fait remarquer, en conclusion, la difficulté d'établir irréfutablement qu'une seule exposition aiguë au chlore gazeux produit des effets à long terme.

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1. Introduction

Chlorine (Cl_2; CASRN 7782-50-5) was the first gas to be used as a chemical warfare agent during the First World War [1]. Today, chlorine is widely used in industry (e.g. oxidizing agent in water treatment; pulp mills) and is one of the most commonly manufactured chemicals in the United States [2]. Chlorine gas may be generated by inappropriate use of household cleaners, resulting in intoxication in residential settings. Chlorine gas has a pungent, irritating odour and is yellowish-green in colour. While chlorine itself is not flammable, due to its reactive nature it can form explosive compounds when mixed with other chemicals such as ammonia. The toxicology literature base is extensive and some general toxicology information is provided in this review. However, the primary purpose of this review is to examine what is known about long term sequelae after an acute exposure to chlorine gas.

2. Acute Effects

The information in this section is primarily derived from clinical and epidemiological studies of human exposure to chlorine gas. The amount of information in the literature from human exposure is large due to chlorine being widely used in industrial processes. In 1995, 25.09 billion pounds of chlorine were produced in the U.S.A. [3]. A National Occupational Exposure Survey conducted in the U.S.A. from 1981 to 1983 estimated that 178,105 people were exposed to chlorine during this three year period [4].

The immediate effects from an acute exposure to chlorine gas have been well documented and are summarized from the Hazardous Substances Data Bank [3], a database of the National Library of Medicine's TOXNET system, Bethesda, MD. U.S.A. Unless otherwise stated, the length of exposure required to cause the observed effect was not indicated in the Hazardous Substances Data Bank.

Exposure Conc.	*Effect*
1 – 3 ppm:	mild irritation
3 – 6 ppm:	itching, stinging, and burning of eyes; lacrimation; blepharospasm; burning sensation of the nose and throat; sneezing; coughing; bloody nose or sputum
5 – 10 ppm:	moderate upper respiratory irritation
10 – 20 ppm:	intense irritation
30 ppm:	chest pain; vomiting; dyspnea; cough

Serious effects resulting from prolonged or very high exposure:

14 ppm:	30 minutes exposure causes severe pulmonary damage
430 ppm or more:	30 minutes can be fatal
34 – 51 ppm:	60 minutes can be fatal
1000 ppm:	fatal within a few breaths

Symptoms of exposure to chlorine gas include rhinorrhea, nausea, headache, dizziness and fainting, muscle weakness, choking, epigastric pain, a feeling of suffocation, apprehension

and anxiety, dermatitis, retrosternal burning and substernal pain, respiratory distress, shortness of breath, pneumonia, bronchospasm and noncardiogenic pulmonary edema [3]. Bronchopneumonia or respiratory collapse may be lethal complications of chlorine exposure. In addition, the symptoms of chlorine gas exposure may be immediate or delayed up to several hours after exposure. Symptoms generally resolve within 6 hours after mild exposures, but may continue for more than 24 hours after severe exposures [3].

Acute inhalation of an irritant gas may result in an asthmatic-type of illness which is called reactive airways dysfunction syndrome (RADS) [5]. The diagnosis of RADS requires the assumption of normal pulmonary physiology and absence of bronchial hyper-reactivity prior to the irritant gas exposure. The pathology of RADS involves a primarily lymphocytic inflammatory response with some evidence of subepithelial thickening and fibrosis. Most patients with this condition who survive the short-term exposure to a toxicant apparently recover completely without significant clinical or physiologic sequelae [6]. Due to the irritant nature of chlorine gas, it is a good candidate for inducing RADS.

The possibility of long-term effects from an acute exposure to chlorine gas has been widely discussed in the literature. One view is that moderate or severe exposure (associated with acute marked airflow obstruction and air trapping) may result in residual pulmonary dysfunction, most notably hyper-reactive airways and low residual volumes and that these long-term sequelae of acute exposure may persist for several years [3]. The other view contends that "long-term complications from chlorine exposure are not found in people who survive a sudden exposure unless they suffer complications such as pneumonia during therapy. Chronic bronchitis may develop in people who develop pneumonia during therapy" [2].

Das and Blanc [7] reviewed several studies [8-14] and noted that residual effects from acute chlorine exposure have been inconsistently observed. The methodologies and follow-up periods varied considerably and the more recent ones [8,12,13] reviewed suggested that airway obstruction or increased non-specific airway responsiveness may persist following acute inhalation injury due to chlorine gas.

The long-term effects observed from acute exposure to chlorine gas have been described in terms of pathology or lung function. Schonhofer et al. [15] concluded that a single high exposure to chlorine gas may lead to acute respiratory injury and to long-term reactive airway dysfunction. Specifically, they observed typical symptoms of inflammatory changes of the airways that had corrected by 16 months post-exposure and non-specific bronchial hyper-responsiveness up to 30 months after the exposure. Shroff et al. [16] evaluated cytopathological changes in 28 individuals exposed to 66 ppm of chlorine gas for approximately one hour. Twenty-five days after the exposure, 25% of the individuals showed evidence of epithelial regeneration and repair by fibrosis and the authors concluded that this could lead to chronic ventilatory incapacitation. One possible outcome of a pathological alteration in the airways could be the development of asthma. Moore and Sherman [17] report the case of a 25-year old man exposed to chlorine gas in an enclosed environment (exposure level not reported). The man developed a persistently debilitating asthma following the exposure. Chester et al. [18] observed detrimental effects on pulmonary lung function as a result of a sublethal exposure to chlorine gas. In another study, pulmonary function was not impaired but an acute chlorine exposure caused impaired neurobehavioural function almost

five years after the exposure [19]. With the exception of one of these studies (Shroff et al. [16]), the concentration of chlorine and duration of exposure are unknown an this will affect the observed outcomes.

Another review [20] discussed the potential sequelae of chlorine exposure and concluded that "virtually all cases of single acute exposures resolve with no long-term sequelae, although most exposures are not intense enough to induce pathological change in the respiratory system". Ploysongsang et al. [21] studied the effects of chlorine exposure at a swimming pool. The patients (n=4) all experienced cough, irritation in the upper respiratory tract and eyes and tightness in the chest. All lung function impairment was temporary and cleared within one month of the exposure. Ploysongsang et al. [21] observed no residual lung damage. A study of 84 individuals who were accidentally exposed to chlorine gas and brought to hospital 30 minutes to two hours after exposure were examined for effects [22]. A majority of the cases had upper respiratory tract effects like cough and irritation in the oropharyngeal region. Bronchospasm was observed in 15 of the 84 cases. Four weeks after the exposure, none of the affected individuals had any residual pulmonary function impairment as measured by spirometry. Barret and Faure [23] observed no long term sequelae as a result of acute chlorine exposure even in patients with abnormal respiratory function tests or blood gases on admission to the hospital immediately post-exposure. Again it should be emphasized that there is very little information on the actual exposure concentrations in the literature.

Further complicating the lack of information on exposure level and duration in the literature of human chlorine exposure is that few studies documented pre-exposure health. Traub et al. [24] reviewed a number of studies and concluded that all were limited by a lack of information regarding premorbid conditions, limiting the conclusions to be drawn. They also discuss one study [25] where before and after pulmonary function testing was performed, but concluded that, even in this semi-controlled study with respect to premorbid conditions, the long-term sequelae of chlorine gas exposure were unclear. The existence of a pulmonary condition prior to exposure, including smoking [7], may affect the observations made after exposure to chlorine gas.

Laboratory inhalation exposures of animals provide for controlled exposure conditions but extrapolation to humans is difficult. Barrow and Smith [26] exposed rabbits to a single, 30 minute atmosphere of chlorine (50, 100, or 200 ppm; 145, 290 or 580 mg/m^3). Lung function was evaluated prior to exposure and 30 minutes, 3, 14 and 60 days after exposure. Most of the pulmonary function endpoints measured returned to normal by 60 days post-exposure with the exception of pulmonary compliance in the rabbits exposed to 100 or 200 ppm. Pathological examination of the lungs revealed no changes in lungs of rabbits exposed to 50 ppm but initial haemorrhage and edema followed by chronic inflammation was observed in lungs of rabbits exposed to 100 or 200 ppm. In another study [27], rats were exposed to 1,500 ppm of chlorine for 5 minutes to assess the time-course of pathophysiological alterations in a model of RADS. The animals were assessed over a 3 month period after exposure by the measurement of lung resistance, responsiveness to inhaled methacholine, histological examination of the airway epithelium, and cytology of bronchoalveolar lavage. The authors concluded that an acute, high chlorine exposure resulted in functional and pathological abnormalities that resolved in the majority of animals after a variable period of time. With both of the studies reviewed, a direct estimate to humans is not possible due to species

differences, specifically breathing patterns (humans are mouth or oro-nasal breathers whereas rodents are obligatory nose breathers) and morphology of the respiratory tract (humans have a regular dichotomous branching pattern whereas it is monopodial in rats and rabbits).

It needs to be pointed out that the exposures used in the animal studies that caused effects were very high (rabbits: 100 and 200 ppm; rats: 1,500 ppm) when compared to the concentration of chlorine required to induce vomiting, coughing and shortness of breath in humans (30 ppm). Species differences between rabbits, rats and humans creates a level of uncertainty such that to start making comparisons a minimum uncertainty factor of ten should be applied to the exposure concentrations. The use of uncertainty factors is widespread in regulatory toxicology to help account for known and unknown variability in response across species. Thus, the exposure levels that resulted in observable effects that resolved over time in the animal studies should be divided by 10 for any initial comparison to humans.

3. Chronic Effects

While there is a significant body of literature that discusses chronic exposures to chlorine gas followed by an acute "gassing" event, a situation that occurs with some frequency in occupational/industrial settings, this review will not address these scenarios. Williams [28] suggested that the major difference between industrial populations who work with chlorine and community residents who have a single exposure is that the industrial workers are at risk of repeated acute exposure incidents against a background of very low exposure. This results in an inflammatory response that persists after an acute gassing, having had no chance to resolve because of the continuous low level exposure.

Das and Blanc [7] observed that chronic exposure data are limited which allows for few general conclusions to be drawn. The studies reviewed dealt with chronic exposures only, i.e. no acute gassing episodes. Several studies have concluded that there are no observable effects from chronic low level exposures to chlorine based on the endpoints studied [29-33]. Other studies have observed health effects attributable to chronic chlorine exposure [34,35].

4. Reproductive/Developmental Effects

No information is available on the reproductive or developmental effects of chlorine gas in humans or animals.

5. Cancer Risk

Chlorine gas was not carcinogenic in mice and rats exposed to varying concentrations of the gas [3], and is not classifiable as a human carcinogen.

6. Guidelines and Exposure Limits

See Annex 1 for explanations of the guidelines.

Military Exposure Guidelines (See Table 1; Annex 1):

1 – Hour MEG Severe = 58 mg/m^3 (20 ppm)
1 – Hour MEG Significant = 5.8 mg/m^3 (2 ppm)
1 – Hour MEG Minimal = 1.5 mg/m^3 (0.52 ppm)
8 – Hour MEG = 1.5 mg/m^3 (0.52 ppm)
14 – Day MEG = 0.29 mg/m^3 (0.1 ppm)
1 – Year MEG = N/A

Acute Exposure Guideline Levels[1]:

For a 10 minute exposure:
AEGL-1 = 0.50 ppm
AEGL-2 = 2.8 ppm
AEGL-3 = 50 ppm

Emergency Response Planning Guideline[2]:

ERPG-1 = 1 ppm
ERPG-2 = 3 ppm
ERPG-3 = 20 ppm

Temporary Emergency Exposure Limits[3]:

TEEL-0 = 0.5 ppm
TEEL-1 = 1 ppm
TEEL-2 = 3 ppm
TEEL-3 = 20 ppm

Threshold Limit Values (TLV)[4]:

TWA = 0.5 ppm
STEL = 1.0 ppm

Permissible Exposure Limit[5]:

PEL = C 1.0 ppm

Recommended Exposure Limit[6]:

REL = C 0.5 ppm [15 minutes]
IDLH = 10 ppm

The original NIOSH Immediately Dangerous to Life or Health (IDLH) guideline was set at 30 ppm based on a 1971 International Labour Office report stating that an exposure to 30 ppm will cause intense coughing fits, and exposure to 40 to 60 ppm for 30 to 60 minutes or more may cause serious damage [36]. This guideline was revised to 10 ppm based on acute inhalation data in humans [37].

7. Conclusions

1. The objective of this review was to describe the known toxicological outcomes of an acute exposure to chlorine gas (CASRN No. 7782-50-5) with respect to long term sequelae.

2. Chlorine is widely used in industrial processes. in the home as a cleaner, and in swimming pools. Thus, the possibility of human exposure to chlorine gas is high.

3. The literature appears contradictory; many investigators observed no effects while others observed long-term effects. This may be partially due to different endpoints being assessed but the contradiction also exists between studies when the same endpoints were measured. Possible explanations for these differences could be the existence of lung disease prior to exposure, or to the effects of smoking. Individuals with either of these conditions may be more susceptible to chlorine exposure. The concentration and duration of chlorine exposure would play a role in the potential for long term sequelae as well. Only one study provided information on the concentration of chlorine (66 ppm for approximately one hour) and it was concluded by the authors that the observed effects could lead to chronic ventilatory problems. This concentration is more than twice the level that would induce vomiting, coughing and shortness of breath.

4. Animal inhalation toxicology studies allow for strict control of both the concentration of the gas and the duration of the exposure. The studies reviewed examined the effects after acute exposures to chlorine and noted that the observed effects may resolve over time. One limitation of animal studies is the difficulty of extrapolating the observations to the human.

5. From the peer-review human and animal literature, it is difficult to conclusively determine if there are long term effects after an acute exposure to chlorine gas.

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Annex 1

The information in this annex is excerpted directly from the references cited.

Table 1. *Definitions of Health Effects Associated with Air-MEGs.* [38]

EXPOSURE DURATION		HEALTH EFFECTS AND PERFORMANCE DEGRADATION
SHORT-TERM	1-hour Severe	The airborne concentration above which continuous exposure for 1 hour could begin to produce life-threatening or lethal effects in a small portion of individuals. Increasing concentrations and/or duration of exposure will increase incidence of lethality and severity of non-lethal severe effects.
	1-hour Significant	The airborne concentration above which continuous exposure for 1 hour could begin to produce irreversible, permanent, or serious health effects that may result in performance degradation and incapacitate in a small portion of individuals. Increasing concentrations and/or duration of exposure will increase incidence and severity of effects.
	1-hour Minimum	The airborne concentration above which continuous exposure for 1 hour could begin to produce mild, non-disabling, transient, reversible effects, if any. Such effects should not impair performance. Increasing concentration and/or duration could result in performance degradation, especially for tasks requiring specific mental/visual acuity or physical dexterity/strength.
	8-hour and 24-hour **	The airborne concentration above which continuous exposure for 8 or 24 hours could begin to produce mild, non-disabling, transient, reversible effects, if any. Such effects should not impair performance. Increasing concentration and/or duration could result in performance degradation, especially for tasks requiring specific mental/visual acuity or physical dexterity/strength.
	14-day	The airborne concentration for a continuous exposure for up to 14 days (24 hours/day) that should not impair performance and is considered protective against significant, non-cancer effects. Increasing concentration and/or duration could result in performance degradation or increase the potential for inducing delayed/permanent disease (e.g., kidney disease or cancer).
LONG-TERM	1 year	The airborne concentration for a continuous exposure up to 1 year (365 days, 24 hours/day) that is considered protective against health effects including chronic disease and increased risk to cancer (i.e., cancer risk greater than 1×10^{-4}). No performance degradation or long-term health consequences are expected with exposure at or below this level. Increasing concentration and/or duration could increase the potential for delayed/permanent disease (e.g., kidney disease or cancer).

* Sensitive individuals may be predisposed to toxic effects and, therefore, maybe more susceptible. If available scientific evidence regarding such subpopulations exists for a particular chemical, then this information is provided in the guideline tables.

** For military unique chemicals warfare agents (i.e., GA, GB, GD, GF, VX, and HD), a 24-hour MEG has been derived instead of a 14-day MEG because of the likelihood for CWA exposures to extend beyond a 24-hour period is extremely small. The definition of effects associated with these values is the same as the 8-hour guidelines.

[1] **Acute Exposure Guideline Levels**, or AEGLs, describe the dangers to humans resulting from short-term exposure to airborne chemicals [39]. The National Advisory Committee (a joint committee between the National Academy of Sciences, U.S. Environmental Protection Agency and the Agency for Toxic Substances and Disease Registry) for AEGLs is developing these guidelines to help federal and local authorities handle emergencies involving spills or other accidental exposures.
The recommended exposure levels are applicable to the general population including infants, children, and other susceptible individuals. The three AEGLs have been defined [39] as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter (ppm or mg/m^3)) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.
AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.
AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that can produce mild and progressively increasing but transient and non-disabling odour, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is an increase in the likelihood of occurrence and severity of effects. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience effects at concentrations below the corresponding AEGL.

[2] **Emergency Response Planning Guidelines.** American Industrial Hygiene Association [40] Emergency Response Planning Guidelines (ERPG) for chemical concentrations in air are designed to assist in the development of emergency response strategies.

ERPG-1 The maximum concentration in air below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild transient adverse health effects or perceiving a clearly defined objectionable odour.
ERPG-2 The maximum concentration in air below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair their abilities to take protective action.
ERPG-3 The maximum concentration in air below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[3] **Temporary Emergency Exposure Level.** The U.S. Department of Energy Temporary Emergency Exposure Level (TEEL) guidelines were developed for emergency responders [41]. TEELs are based on the Emergency Response Planning Guidelines[2].

TEEL-0 The threshold concentration below which most people will experience no appreciable risk of health effects.

TEEL-1 The maximum concentration in air below which it is believed nearly all individuals could be exposed without experiencing other than mild transient adverse health effects or perceiving a clearly defined objectionable odour.

TEEL-2 The maximum concentration in air below which it is believed nearly all individuals could be exposed without experiencing or developing irreversible or other serious health effects or symptoms that could impair their abilities to take protective action.

TEEL-3 The maximum concentration in air below which it is believed nearly all individuals could be exposed without experiencing or developing life-threatening health effects.

For application of TEELs, it is recommended that the concentration at the receptor be calculated as the peak 15-minute time-weighted average concentration. It should be emphasized that TEELs are default values, following the published methodology as described by the Subcommittee on Consequence Assessment and Protective Actions (SCAPA) [42]. SCAPA was established by the Emergency Management Advisory Committee (EMAC) of the U.S. Department of Energy (DOE) to assist the Director of Emergency Management (DEM).

[4] **Threshold Limit Value.** American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV) are guidelines used by professional industrial hygienists [43]. The values are intended for use only as guidelines or recommendations to assist in the evaluation and control of potential workplace health hazards. Further, these values are not fine lines between safe and dangerous conditions. TLVs are not regulatory or consensus standards and if any of these TLVs are exceeded, a potential hazard from that substance is presumed to exist.

Threshold Limit Value—Time–Weighted Average (TLV–TWA). The TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. Although calculating the average concentration for a workweek, rather than a workday, may be appropriate in some instances, ACGIH does not offer guidance regarding such exposures.

Threshold Limit Value—Short-Term Exposure Limit (TLV–STEL). A 15-minute TWA exposure that should not be exceeded at any time during a workday, even if the 8-hour TWA is within the TLV–TWA. The TLV–STEL is the concentration to which it is believed that workers can be exposed continuously for a short period of time without suffering from 1) irritation, 2) chronic or irreversible tissue damage, 3) dose-rate-dependent toxic effects, or 4) narcosis of sufficient degree to increase the likelihood of accidental injury, impaired self-rescue, or materially reduced work efficiency. The TLV–STEL will not necessarily protect against these effects if the daily TLV–TWA is exceeded. The TLV–STEL is not a separate, independent exposure guideline; rather, it supplements the TLV–TWA where there are recognized acute effects from a substance whose toxic effects are primarily of a chronic nature. Exposures above the TLV–TWA up to the TLV–STEL should be less than 15 minutes, should occur less than four times per day, and there should be at least 60 minutes between successive exposures in this range. An averaging period other than 15 minutes may be recommended when this is warranted by observed biological effects.

[5] **Permissible Exposure Limit.** The Occupational Safety and Health Administration (OSHA) in the U.S.A. sets permissible exposure limits (PEL) based on a time-weighted average over an 8-hour workday and a 40-hour workweek [44]. OSHA ceiling concentrations (as indicated by a "C" preceding the value) must not be exceeded during any part of the workday. If instantaneous monitoring is not possible, the ceiling must be assessed as a 15-minute TWA exposure.

[6] **Recommended Exposure Limit.** The National Institute for Occupational Safety and Health (NIOSH) in the U.S.A. sets Recommended Exposure Limits (RELs) and Immediately Dangerous to Life or Health (IDLH) guidelines based on available data, human and/or animal, for hundreds of chemicals [44]. Unless noted otherwise, RELs are time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek. A short-term exposure limit (STEL) is designated by "ST" preceding the value; unless noted otherwise, the STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday. A ceiling REL is designated by "C" preceding the value; unless noted otherwise, the ceiling value should not be exceeded at any time. The current NIOSH definition for an IDLH exposure condition is a condition "that poses a threat of exposure to airborne contaminants when that exposure is likely to cause death or immediate or delayed permanent adverse health effects or prevent escape from such an environment." The purpose of establishing an IDLH exposure concentration is to "ensure that the worker can escape from a given contaminated environment in the event of failure of the respiratory protection equipment."

List of Acronyms/Units

AEGL	Acute exposure guideline level
CASRN	Chemical Abstracts Service registry number
CWA	Chemical warfare agent
ERPG	Emergency response planning guideline
GA	Tabun
GB	Sarin
GD	Soman
GF	Cyclosarin
HD	Sulphur Mustard
IDLH	Immediately dangerous to life or health
MEG	Military exposure guideline
mg/m^3	milligrams per cubic metre
NIOSH	National Institute for Occupational Health and Safety
OSHA	Occupational Safety and Health Administration
PEL	Permissible exposure limit
ppm	Parts per million
RADS	Reactive airways dysfunction syndrome
REL	Recommended exposure limit
STEL	Short term exposure limit
TEEL	Temporary emergency exposure limit
TLV	Threshold limit value
TWA	Time weighted average

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Chlorine (Cl_2; CASRN 7782-50-5) was the first gas to be used as a chemical warfare agent during the First World War and is widely utilised today in industry (e.g. oxidizing agent in water treatment; pulp mills). The immediate effects from acute exposure are well documented but the long term sequelae from an acute exposure are not well understood. Several studies were reviewed that discuss the long term outcome of an acute exposure to chlorine gas and their conclusions appear contradictory. This may be due to different endpoints being assessed, to the existence of lung diseases prior to exposure, or even the effects of smoking. The concentration and duration of chlorine exposure would also play a role in the potential for long term sequelae and few of the studies reviewed provided this information. Animal inhalation toxicology experiments that studied the potential for long term effects after an acute exposure to chlorine noted that the observed effects may resolve over time. An intrinsic limitation of animal studies is the difficulty of extrapolating to humans. Thus, from peer-review human and animal literature, it is difficult to conclusively determine if there are long term effects after an acute exposure to chlorine gas.

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